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# The Cure of Sleeping Sickness

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# CURE OF SLEEPING SICKNESS.

The *Times* of Friday, August 25th, 1922, contained a report from Hamburg headed "Cure of Sleeping Sickness, German Dream of Colonial Empire," dealing with the discovery of the new drug called "Bayer 205," regarding which extravagant claims were advanced.

A certain Dr. Zache, a former District Governor in German East Africa, is quoted as stating that the introduction of this synthetic preparation will place the key of Africa in German hands. Again, at a meeting of "the Association of Tropical Medicine," where scientists from Holland, Java, Turkey, South America and Germany met in conference, the opinion was expressed that Germany had made a discovery of tremendous importance. Indeed, it is stated that one of the speakers, whose identity has not been revealed, affirmed that "Bayer 205," being the key to tropical Africa, is consequently the key to all the colonies. It was therefore necessary, he continued, to safeguard this discovery for Germany. So great was its value that any privilege of a share in it granted to other nations must be made conditional upon the restoration to Germany of her colonial empire.

In a short leading article entitled "Deutschland über Alles," the *"Times"* commented on the pronouncements and on the fact that in the utterances of the medical men there was nothing about the benefit which the remedy would bestow upon humanity. Germany alone was considered, and the drug was lauded chiefly because it would prove a lever whereby that country might regain possession of her colonies. It was also pointed out that the statements made were absurd, and that there was some reason to think that the secret of the new remedy was not as great a secret as the German doctors imagined.*

It is clear that, whatever may be the value of the discovery,

*It is only fair to state that when this article was in the Press a statement by Dr. B. Nocht, the distinguished Director of the Institute of Tropical Medicine at Hamburg, appeared in the *Archiv für Schiffs-und Tropen-Hygiene Pathologie und Therapie Exotischer Krankheiten.*

Professor Nocht emphatically denied that there was a single word of truth in what the *Times* said regarding the German view of "Bayer 205." Indeed, he remarks that the subject of "Bayer 205" was not even discussed at the Hamburg conference.

we have here an interesting situation which merits, nay demands, careful enquiry. At the outset it is well to bear in mind the fact that history repeats itself. Those who remember the introduction of tuberculin by Koch will recall the furore which his discovery created, the wild statements made regarding it and the false hopes excited. In those days we were less critical of the Germans. They were undoubtedly whole-hearted workers in the cause of Science, they had contributed notably to the welfare of humanity, and in some directions we were content to sit at their feet and accept their bacteriological teachings. Eventually tuberculin found its place in our diagnostic and therapeutic armature, a useful one, doubtless, but very different from that which had been assigned to it by the enthusiasts of the day, those ill-balanced folk who, like the poor, are always with us, and who, like the Athenians of old, are ever seeking after some new thing. A very similar situation arose when Ehrlich introduced his famous "606" or salvarsan.

Now we have come to distrust, not perhaps the individual German, but the spirit of a land which has been cursed by militarism, which has apparently forgotten some of her old traditions, and which naturally resents the position into which the folly of her rulers and the mad lust for world power has placed her. Yet there are useful lessons to be learned from the opinions expressed by the patriotic, if narrow-minded, German medical man who, so far as this country is concerned, remains incognito. For one thing, they seem to show, as the *Times* points out, that the German political view has not altered, for another they indicate, in no uncertain fashion, the vast and far-reaching importance of tropical disease as a factor in the development, not only of Africa, but of all countries blessed or cursed with a warm climate ; for yet another they must, whether we like it or not, make us take counsel with ourselves and see if there is anything lacking in our scientific constitution, in our training, our methods, our resources, which enables the German to boast, with some show of reason, that in matters chemotherapeutical his nation leads the world.

Sir William Pope has already raised his voice, and in an article contributed to the Journal of the Society of Chemical Industry, has attempted to review the situation, has found Great Britain wanting from the chemical standpoint and has suggested a remedy. Unfortunately, Sir William Pope is evidently not fully conversant with all that has been accomplished in this country as regards the treatment of African sleeping sickness. He does not seem to be aware that sleeping sickness, at least in one of its forms, is a curable disease, that many cases have

been cured, and that a very considerable share of whatever credit attaches to this accomplishment is due to the researches of French and British workers.

At present atoxyl, a form of organic arsenic, together with antimony, constitutes the standard treatment for human sleeping sickness. Atoxyl was introduced by Thomas, of Liverpool, and first used in the disease by Kopke, of Portugal, while so far as the antimony part of this therapy is concerned observers in our country led the way. Again, a vast deal has been done in India and the colonies to combat the various trypanosome infections of animals, but apparently Sir William Pope is not adequately versed in these researches.

There are doubtless many people in Sir William Pope's position and many others who know far less than he does about the whole question. Hence it seems desirable to give a brief account of African sleeping sickness, that old negro lethargy, well known in the days of the slave ships but of late years unhappily confounded in the public press, and to some extent in the public mind, with another so-called sleeping, or rather sleepy, sickness. The latter is not specially an African or tropical disease, is in many respects quite unlike true sleeping sickness, may have some association with influenza, is still obscure as regards its etiology and is better named lethargic encephalitis. Thereafter, it will be convenient to discuss the new remedy, to hazard an opinion as to its chemical constitution, to recount the experimental work done upon it, to mention the clinical tests which have been applied to it, to appraise, so far as is possible, its true value and significance, and *inter alia* to consider the lines on which Germany is at present working in connection with her remarkable propagandist programme in the realms of tropical medicine and hygiene.

Finally, something may be said regarding the position of this country, Sir William Pope's scheme, and the necessity of recognising, not only the important part the prevention and cure of tropical disease plays politically, both within and without the confines of the British Empire, but the need for a general quickening and for a special training in research. This is especially the case in connection with chemical and bio-chemical problems as they bear upon the maladies of the tropics.

African sleeping sickness is a human trypanosomiasis, that is to say it is an infection with the lowly protozoal animal parasites called trypanosomes, the word being derived from the Greek τρύπανον borer, and σωμα body. It is rather a fitting nomenclature, as anyone must confess who has seen the eel-like parasites boring their way through a mass of red blood

cells. This is, as a rule, easily demonstrated when a drop of the blood of a heavily infected case is examined fresh under the high powers of the microscope. The wriggling and writhing colourless parasites butt and push vigorously amongst the cells, but they do not actually bore into them as do the tiny malarial spores. These trypanosome are flagellates, that is to say each possesses a flagellum or whip-like extension from the body. It resembles a tail, a flexible tail, which can be thrown into sinuous curves, but unlike a tail it is situated anteriorly, not posteriorly, and it is owing to its impelling power that the active parasite darts hither and thither. A membrane or fringe, not unlike the back fin of a conger, runs well nigh the whole length of the parasite and gives it a very characteristic appearance, well shown in the beautiful wax and gelatine models at the Natural History Museum, South Kensington.

The trypanosomes are not only found in the blood. They invade the lymphatic system and occur in the lymph glands. Eventually they get into the central nervous system, find a habitat in the spinal fluid and also invade the brain. Though very tiny, they exist in great numbers, and, like other protozoal parasites, produce a toxin or poison which exercises a dire effect on the human organism.

Trypanosomes were known in animals long before they were found in man. Indeed, many animals harbour perfectly harmless species. The first pathogenic trypanosome was discovered by Evans in India in 1880, who found the parasite, now named after him, in the blood of horses suffering from the disease called surra.

Long ago, in 1734 to be precise, a certain John Atkins in a book called "The Navy Surgeon" mentioned a disease, common on the Guinea Coast, which he called "the sleeping distemper." In 1803 a naval surgeon, Winterbottom, observed and recorded the enlargement of glands in the necks of negroes suffering from this malady. He emphasized its importance as an aid to diagnosis. A few years later Moreau de Jonnès described sleeping sickness amongst slaves in the Antilles, and thereafter many cases were reported in Africa and elsewhere. It was not, however, until 1890 that Nepveu found a trypanosome in human blood, but he did not realize the importance of his discovery, and his description of the parasite was very imperfect. In 1901 Forde, a colonial medical officer, came across a trypanosome in the blood of a patient from the Gambia. Fortunately he showed it to a trained observer, the late Dr. Dutton of the Liverpool School of Tropical Medicine, who was able to place and name the parasite correctly. Dutton found a simi-

lar organism in a similar type of case from the same colony and christened the parisite *Trypanosoma gambiense*. It was soon evident that this trypanosome infection was not uncommon, and that it was associated with a peculiar form of fever accompanied by wasting.

In the meantime work had been started in Uganda, where sleeping sickness had assumed formidable proportions, due possibly, though the point has never been definitely settled, to the infection of a non-immune population as the result of the opening up of Africa by Stanley and the establishment of trans-continental trade routes. Indeed, Sir Patrick Manson once stated at a dinner that Stanley, who was present, had been responsible for the deaths of half a million of people. Stanley, a tired and worn man, merely smiled and shrugged his shoulders.

In Uganda Dr. Castellani found the parasites not only in the blood but in the cerebro-spinal fluid of patients, and suggested that they were the cause of sleeping sickness. Confirmation was soon forthcoming. Bruce, who in 1894 had proved the fell disease of cattle and horses in Zululand, that nagana, dreaded alike by the settler, the explorer, the elephant hunter and the native, to be due to a trypanosome eventually named after him, was put in charge of a Commission which worked out the problem. They showed that, as Sambon and Brumpt had already predicted, the dusky tsetse fly, *Glossina palpalis,* was the vector of infection. It was left, however, to Kleine to demonstrate that in the fly the parasite passes through a definite cycle of development, that it is no mere question of mechanical transmission.

The next item of importance was the discovery by Stephens and Fantham that the form of sleeping sickness in Rhodesia was due to a trypanosome distinct from *T. gambiense* and which was named *T. rhodesiense*. It produces a very grave type of the disease, and there has been much discussion as to whether or not this trypanosome is really the *T. brucei* of horses and cattle which has recently acquired properties making it pathogenic to man. However that may be, Kinghorn and Yorke have shown that, like *T. brucei,* it is carried by the grey tsetse fly, *Glossina morsitans,* which hitherto had only been associated with animal trypanosomiasis.

Many interesting matters have been elucidated about the human disease, and much work has been done on its relation to the big game of Africa, but here it is only necessary to mention that of late years a human trypanosomiasis has been found to exist in Brazil and other regions of South America. There the insect vector is a species of nocturnal biting bug, and the ani-

mal reservoir is the armadillo. The disease, a most peculiar and interesting one, in no way resembles African sleeping sickness, though the causative parasite is not unlike that which produces negro lethargy.

And now a note as to the symptoms of the latter. At the start the disease is insidious. There is fever, there may be a skin rash. Local swellings, local changes in sensation may be noted. The heart may be a little affected, the spleen may enlarge. Slowly the patient gets weaker; he suffers from headache, his lymph glands, especially those in his neck, become enlarged. Soft at first, as they shrink they grow hard and dense. There is some anæmia, and in the European there is pallor. The parasite is present in the blood, the patient has trypanosomiasis only. He may occasionally recover without any treatment. As a rule, however, in some four to eight months, though it may not be for years, there is evidence of an involvement of the central nervous system. This may begin with acute, even fulminating, symptoms, but usually the malady fastens gradually but surely upon its victim. He gets weaker, he gets dull. He shuffles when he walks and he shuffles slowly. His face becomes puffy, and he looks sulky and silly. Anon he is drowsy, is seized with tremors, and his cephalgia increases. Sometimes, indeed, the headache is very severe, splitting and blinding in its intensity. The hapless patient continues febrile and slowly becomes a hopeless invalid, helpless and indifferent to his surroundings, though he can be roused to speak and swallow. Later on he will fall asleep with half chewed food in his mouth, and all the time he emaciates, while his tremors increase and his neck muscles grow rigid. Then his skin begins to suffer, as it does in most wasting diseases; paralysis may ensue, the face becomes bloated, saliva dribbles from the mouth, and the end is sad and terrible if pneumonia or dysentery do not bring welcome relief.

Such is the ordinary course of untreated sleeping sickness as it occurs in Uganda or the Belgian and French Congo or the Southern Sudan.*

The uninitiated were wont to say: "Sleeping sickness, now that is what we should like to die of." Those with any knowledge of sleeping sickness camps will scarcely echo this pious wish, for, at certain of its stages at least, sleeping sickness is far from being a painless disease either to the unfortunate victim or to the beholder of his sufferings.

*Quite recently Archibald, in cases of sleeping sickness from the Bahr-el-Ghazal, has found a trypanosome which is apparently *T. rhodesiense.*

Naturally, as soon as its precise nature was known, determined and strenuous efforts were made both at prevention and cure, and in both these directions help was forthcoming from the experience gained with the various trypanosome affections of stock, which are of immense economic importance. Indeed, since the devastating human outbreak in Uganda spent its force or was checked the animal trypanosomiases have bulked more largely than the disease in man. For one thing they are not confined to Africa, for another they are more widespread, for yet another, sad to say, a malady which adversely affects the pocket sometimes excites more interest than one which plays its chief rôle as a destroyer of native life.

And yet, even from the standpoint of the economist, sleeping sickness is by no means negligible, for it limits our labour forces and, when in epidemic form, will indirectly turn the fertile land into a waste and howling wilderness, as witness what has happened on certain of the islands of the Victoria Nyanza. Nor is this epidemic danger at an end. At present the signs are distinctly disquieting. Sleeping sickness is far from being asleep. It is a force which has to be reckoned with, and therefore any hope of material help in the campaign against it is sure of a welcome by those who realize its potentialities for evil. It is unnecessary to recount all that has been done in the way of treatment, the remedies tried and discarded, the failures and the successes.

It will suffice here to consider more particularly the new drug which has appeared and has given rise to so much excitement and to remarkable Teutonic prophecies. Before doing so, however, we may ask what are the properties which an ideal cure for sleeping sickness would possess? These are easily listed. It should be effective not only in the way of abolishing trypanosomes from the blood and lymph glands of early cases and from the central nervous system as well in the advanced stages of the disease, but it should do so thoroughly and completely in such a way that relapse, that bugbear of many tropical maladies, does not occur. It should be non-toxic to the patient, that is, while it slays the parasite it should spare the host. So far the chief drugs employed—atoxyl, antimony, salvarsan and its allies—have not been free from an element of danger. It should be readily soluble in water without decomposition, capable of being sterilized without undergoing change, and easily administered, preferably by the mouth. It should be stable, that is to say it should keep well even under adverse tropical conditions, and it should be cheap. If it can be used prophylactically as well as curatively, so much the better. In short, it should be an Ad-

mirable Crichton amongst medicines. Let us see if this has been found.

The first whisperings anent "Bayer 205" were heard in 1919, when it was bruited abroad that a new trypanocide with remarkable properties had been produced by the Bayerische Farbwerke of Leverkusen, near Cologne, which, it was announced, would not be patented in order to avoid information leaking out as to its nature and method of preparation. Incidentally this attempt at secrecy is interesting because in 1915 the Germans scouted the notion that salvarsan, Ehrlich's famous "606", could ever be produced outside the Fatherland and yet it was manufactured in England and elsewhere in large quantities throughout the war and is still being made in this country. Perhaps it was partly on this account that the composition of "Bayer 205" remained shrouded in mystery. The reason advanced by Haendel and Joetten, who apparently were the first to write authoritatively on the new product was the unprotected condition of German industries in foreign countries. Their description of the substance in 1920 indicated an entirely new development in chemotherapy. Here was a synthetic chemical possessing most, if not all, of the desiderata above mentioned. It was described as a white powder easily dissolved in saline solution or distilled water, of neutral reaction, possessing no smell and having a slightly bitter taste. It was stated to be stable and capable of sterilization without deterioration or change. The authors announced that it had an amazing trypanocidal action, minute doses rapidly clearing infected laboratory animals of trypanosomes. Moreover, a point of great importance, it was said to be of low toxicity, the relation of the curative to the toxic dose being as 1 to 40 or more. It was declared to act on the parasites not only in the animal body but in the test tube, that is to say when they were under cultural conditions, and amongst other trypanosomes tested and found susceptible, *T. gambiense* was mentioned. Strange to relate, the common non-pathogenic trypanosome of the rat and the parasite of South American human trypanosomiasis were unaffected by it.

Needless to say an announcement of this kind excited great interest and the statements made were quickly put further to the proof, both in the laboratory and in the case of patients. Mayer and Zeiss, working at the well-known Institute of Tropical Medicine at Hamburg, carried out an extensive series of laboratory experiments, confirmed in many respects the results of Haendel and Joetten, and extended our knowledge in several directions. They found amongst other things that the drug

checked the multiplication of the parasites which, as has long been known, is effected by longitudinal division of their bodies. They put the ratio of curative to toxic action, the so-called chemotherapeutic quotient, at 1 to 167, that of atoxyl being as 1 to 2. Moreover they showed the drug was active whether given under the skin, into the veins, or, a more important matter, by the mouth .and they also demonstrated that it possessed to some degree a preventive action, for animals treated with fairly large doses could not be infected for some months after receiving the drug. Other points which need not here be considered were elucidated, but the crucial test had still to come, the treatment of a case of human sleeping sickness. However, before this was accomplished the same authors put human beings to a harmless and interesting test. They had found that the protective action of the remedy was due to the fact that it remains for months in an active form in the body. Indeed, it can be demonstrated in the fluid portion of the blood—the serum—and this medicated serum was found to possess curative properties. Hence it occurred to them to administer the "205" to healthy human beings and see if their serum would become trypanocidal (destructive to trypanosomes). They found this to be the case and incidentally proved also that the drug could be given safely to man, at least in small doses over a short period.

Then came the chance of treating a human case of trypanosomiasis and Muehlens and Menk took advantage of it. A man hailing from Fernando Po and infected with *T. gambiense* turned up at Hamburg in March, 1920. He was in the early stage of the disease and was treated cautiously with two small intravenous doses given at an interval of seven days. He stood the drug well, and, after the first injection, the trypanosomes vanished from his peripheral blood for a short time, but they reappeared. The second dose had little effect on them and, as they tended to increase, antimony was substituted for the "205." The patient returned to Africa, and his further history is unknown. Later experience points to the failure being due to the smallness of the doses given, and this error was corrected in the second case which came under observation and which in its way has become classical.

Professor Warrington Yorke of the Liverpool School of Tropical Medicine had a case of *T. rhodesiense* infection under his care. The man, a European, had been treated with arsenic and antimony in various forms, including atoxyl and tartar emetic, but his infection proved resistant. As his condition grew steadily worse he was sent to Hamburg in July, 1921, and

there underwent a course of "Bayer 205", which was given in considerably larger doses than in the first case. The result was remarkable and gratifying considering that the patient was in almost a dying condition. He was to all intents and purposes completely cured, and it appears he has remained in good health ever since. A Belgian doctor has also been cured by a similar dosage, *i.e.* 4 injections, in all amounting to 3·5 to 4 grammes of the powder. He is now back at work, fighting in the Congo the sleeping sickness from whose clutches he has been rescued. The only fly in the ointment, and the fact is not without significance, is that when the drug was pressed signs of kidney irritation showed themselves, so that it was considered better to discontinue it, especially as it had apparently—as events proved, in reality—accomplished its good work.

Here indeed was a triumph for the Germans, and the German preparation and its examination was taken up with renewed zest, not only in Germany but in France and England, by those fortunate enough to get hold of it. For a time work was confined to strains of animal trypanosomes. Wenyon, a leading medical protozoologist in London, confirmed the German results so far as *T. equiperdum* infection in mice is concerned, this trypanosome being the parasite of a peculiar trypanosomiasis of equines called dourine, transmissible not by biting flies but by coitus. Brumpt and Lavier repeated the work on *T. brucei* and *T. rhodesiense,* and obtained satisfactory results in the case of mice and rabbits. Then, as a few Germans had already done, they extended their researches to a different class of parasite altogether, but here encountered failure.

It is not necessary to recount all the experimental work which has been carried out up-to-date. Mayer has reviewed the whole subject quite recently in the *Deutsche Medizinische Wochenschrift* and cites several points not hitherto mentioned. Thus, while most remedies are only effective (in experimentally infected animals) in the first days of infection, "Bayer 205" will save the animal if administered a short time before the period when death might be expected to occur. It can be given by intrathecal injection, that is to say into the spinal canal, a point in its favour, and animals cured by it are immune for many months, not only to the species of trypanosome with which they were infected, but to well nigh all other kinds. This is a most remarkable property, hitherto unknown among trypanocidal agents. In addition to blood serum the milk of treated animals was found to possess protective powers. The albuminuria which it may produce is apparently not of a serious

type and horses are found to be the animals most susceptible to its ill-effects.

It may be stated that cases of human sleeping sickness have now been treated with "205" at the London School of Tropical Medicine, but the results, which will be awaited with interest, have not yet been made public.*

Attention should, however, be directed to a new development. As there was little clinical material obtainable in Germany, that country approached the British Government for permission to send two well-known workers with African experience, Drs. Kleine and Fischer, to Northern Rhodesia in order to get the drug fully tested in the field. It must be remembered that laboratory research, however helpful and fruitful, does not always prove a sure guide as to what happens in nature. The British Government, without any haggling or bargaining, granted the request; the German doctors, accompanied by a laboratory assistant, Fräulein H. Ockelmann, proceeded to Africa, and, thanks to the courtesy of the Director of the Tropical Diseases Bureau, a copy of their first report, has been available.

Dr. Kleine, however, has expressed a desire that the results which he and his colleagues have so far obtained should not yet be published in any form.† Hence all that can be said at present is that while "Bayer 205" is undoubtedly a remarkable remedy, perhaps the most promising hitherto produced for the treatment of sleeping sickness, it is still on its trial. It possesses certain disadvantages, and some of the praise lavished upon it has not been justified as the result of continued observations. Still we may be grateful for its introduction and the laborious work which led up to its discovery. The latter, valuable in itself, also points the way to further developments, but all the same "Bayer 205" is certain-

*The report of Drs. Kleine and Fischer has just been published in the form of an article in the *Deutsche Medizinische Wochenschrift* for December 22, 1922, and is entitled "Bericht über die Prüfung von 'Bayer 205' in Afrika."

†Since the above was written Drs. Low and Manson-Bahr have published a paper on the results of treatment of nine cases of human trypanosomiasis with "Bayer 205". Of these nine cases one died of cerebral trypanosomiasis, seven are apparently cured, while in one (the only example of *rhodesiense* infection) the result has been inconclusive. The authors gave much larger doses than had hitherto been administered, and consider that the appearance of albumin and casts in the urine should not militate against pushing the drug. Their conclusion is that, while "Bayer 205" is not infallible, it is by far the most powerful trypanosomicidal substance so far tested.

ly unlikely to be the key which will unlock for Germany the closed doors of her late possessions in Africa.

And now let us try to get some idea as to the nature of this new drug. It may be said at once that it is no easy matter for laymen, or the ordinary physician, or even for the tropical expert unless he possesses knowledge of a very specialised kind, to understand the intricacies of organic chemistry, and more especially the formulæ of those complex bodies which are now so largely used as therapeutic agents. Still less is it easy to explain their composition in simple language which can be understood by the man in the street. In the present instance recourse has been had to a distinguished chemist in the person of Dr. T. A. Henry, who in a private communication says :—

"It is impossible to explain in simple non-technical language how the production of these synthetic chemicals is achieved but it may perhaps be illustrated by a case involving fairly familiar things. The well-known disinfectant, formalin, is a solution of formaldehyde in water. Formaldehyde has the same elementary composition as the simplest sugars, e.g., glucose, and it can by a simple laboratory operation be converted into a sugar, without any change in its elementary composition, *i.e.*, it still consists, judging from analytical results alone, of one atom of carbon, two atoms of hydrogen and one atom of oxygen, but in the process six molecules of formaldehyde have been condensed and re-arranged into a new molecule which has the characteristic properties of a sugar. After long study of such things the chemist is able to associate a particular type of arrangement of carbon, hydrogen and oxygen atoms with the characteristic properties of a sugar. Within this type there may be endless variations but so long as the type is preserved, the substance produced will be sugar-like. The word sugar to the chemist therefore connotes not the ordinary substance of our breakfast tables but a type of which ordinary sugar is one variant. In the same way the property of colour is associated with particular types of molecular structure in organic compounds and so thoroughly has this subject been investigated that it has become possible to estimate in advance the colour a substance will have when it has been synthesised."

Proceeding to discuss the similar progress which has been made in connection with the physiological action of synthetic chemicals he points out how infinitely more difficult is the problem, for it is one thing to produce a germicide which will kill the most virulent of disease parasites cultivated in test tubes, but quite another to discover a parasiticide harmless to the living host and yet able to reach and slay the same micro-organisms lurking possibly in the recesses of the host's body.

"It has long been known," he continues, "that many of the disease parasites have a selective capacity for dyes and certain of them are identified microscopically by the fact that they are stained by one but not by others. This led naturally to the idea of trying the action of these dyes on the living cultivated parasites in the

hope that the dyes themselves might be toxic to the parasites or, if not, that they might be made the means of carrying toxic substances into the parasites. Working in this way, Ehrlich and Shiga in 1904 showed that a dye called trypan red was toxic to trypanosomes. It was introduced for the treatment of sleeping sickness but did not prove successful. The molecular structure of trypan red being known, two French observers, Mesnil and Nicolle, set to work to determine what variant on the general structure represented by trypan red determined the maximum trypanocidal effect and their results, which were published in 1906, showed that another related dye, trypan blue, represented about the most active trypanocide built on these lines up to that time. About 1914 the makers of 'Bayer 205' began to take out patents for variants on this primary structure and it is clear from the number of patents taken out that the German firm have devoted chemical and pharmacological work to the investigation of the therapeutical possibilities of this group of substances and it is fairly probable that the new drug belongs to this type.

From the contents of these patents it seems clear that the trypanocidal properties are developed independently of the development of colour for some of the most promising products in this series are, like 'Bayer 205' itself, colourless although the line of work suggested above begins with a dye."

"Bayer 205" which, as Mayer stated, contains neither mercury, arsenic, nor antimony, belongs, therefore, to what we may call the benzidine dye series, the characteristic variable of the whole group being a body with the startling name of aminonaphthalenedisulphonic acid. Although its title is possibly forbidding, its formula is comparatively simple, but we need not pursue the subject in further detail. Those who wish to do so will find Dr. Harold King's paper in the *Reports of Applied Chemistry* for 1921 specially illuminating.

The discovery of "Bayer 205," as indeed its name suggests, is largely due to persistence. Presumably 204 substances had been made and tried before it was reached, just as Ehrlich and Hata worked through 605 before they attained to salvarsan. Persistence is not peculiarly a German attribute, but there can be no doubt that the Germans are very patient and persevering workers, especially along chemical lines. The wisdom of the Bayer firm, now, by the way, the Elberfelder Farbenfabriken, is shown by the manner in which, metaphorically speaking, they have stuck to their guns. Long ago they started research on the benzidine colours, and when others were lured from the study of these substances by the advent of atoxyl, salvarsan and other preparations of organic arsenic, or by the counter-attractions of antimony and later of bismuth, they never wholly relinquished the dye quest and so arrived at something valuable, not by any miraculous process, but by the diligent pursuit of well-known methods on sound lines.

We have the necessary skill in this country, but at present some of our skilled workers are, sad to say, unemployed. In addition to persistence, which still exists amongst us as it always has done, we require time and money for the elucidation of these problems. It is slow work and possibly dull work, laboriously ringing the changes on product after product. Unless the chemist is fortunate he may spend months and years in fruitless, or apparently fruitless, endeavour. Naturally a keen and ambitious man finds such work irksome. After all, our organic chemists are not too well paid, and many of them perforce work not so much for filthy lucre as for love of their subject, the satisfaction of advancing the cause of Science and at the same time gaining, quite legitimately, personal "kudos" from their researches, and the respect, possibly even the admiration, of their fellow workers. Hence to get the best results the posts of those engaged in such researches should be made as attractive as possible and every encouragement afforded them to pursue their studies to definite conclusions.

But more than this is required, as Sir William Pope very truly remarks. Of late years there has been a stirring of dry bones and on the medical and pharmacological sides a great impetus to co-ordinated work has been given by the establishment of the Medical Research Council. Our chemists, however, still work far too much in water-tight compartments, and the fascinations of chemo-therapy are known to few of them. Hence Sir William Pope's scheme of an Advisory Council of Chemists acting under Government and charged with drawing up a definite programme of work, with, as its natural corollary, the provision of facilities for promptly making compounds under the Council's direction, merits careful and sympathetic consideration.

He says that there already exist the means for testing the therapeutic action of the products. This is true up to a certain point, but there is scope for great development in this direction, for there is a notable lack of skilled medical protozoologists, and these are badly needed when it is a question of studying trypanosomes and similar organisms. It is curious how few of our younger men think of taking up medical protozoology, and yet it is a fascinating field. The fault is probably to be found in the defective zoological training of the medical student. To be really first class the medical protozoologist should also be a naturalist, but, short of this, a very efficient worker can be obtained if, at an early date, he is made familiar with the nature and significance of those animalcules which have been found to play so great a part in human tropical pathology.

We want men who, amongst other things, can do work of the kind recently recorded by Steffan of Hamburg in the *Zeitschrift für Hygiene und Infektionskrankheiten* for September, 1922. In this paper a careful account is given of the changes produced in trypanosomes by the action of atoxyl and of a number of trypanocidal dyestuffs. "Bayer 205" receives attention and is shown to act on the cell protoplasm of the organisms. In addition to checking division and multiplication it is then a definite poison. Its action is compared with other substances, some of which have a special affinity for the nuclei and blepharoplasts of trypanosomes, those chromatin-bearing portions which play an important part in reproduction.

It is too much to ask that the average medical student should be given fuller instruction in organic chemistry. The poor wretch is already crammed to bursting point with a regular *olla podrida* of information. Indeed, it may well be said of him :—

> And still the wonder grows
> That one small head can carry all he knows—

or perhaps we should say all he is expected to know. At the same time his attention might with advantage be directed to the practical applications of organic substances and to the part they now play in the war against disease and death. The medical man himself might take more interest in the matter, and tropical workers might concentrate more on those problems which are really urgent and the solution of which mean much to us as an Empire.

Money is needed. It is found, *mirabile dictu,* even in these days, for the conquest of Mount Everest. Folk always seem willing to raise funds for the exploration of the Antarctic, a fact Maxwell, the novelist, faithfully records in his "Spinster of this Parish," but somehow or other few people beyond John Rockefeller appear to care much about these truly great and pressing questions upon which so much depends.

Persistence, time, money. Is there anything else? Assuredly, for we require far-sightedness and earnestness. Far-sightness should be a characteristic of our rulers, of those responsible for running the Empire, but in medical and sanitary matters it is not forthcoming to any great extent. We might well take a leaf out of the German book. Driven out of their colonies, where, by the way, it is only fair to state some of their medical and sanitary arrangements were very creditable, they cast their eyes on South America and other lands. Forthwith there appeared an excellent series of guides, the *Auslandswegweiser* issued by Friedrichsen and Co., of Hamburg,

full of all kinds of useful information and containing volumes on tropical hygiene and the care of health in the tropics. Now there is little doubt that this country would have done just the same if she had been placed in a similar position. Not only so, but she would probably have done it better. Consider how we beat the Germans at their own game of making and using lethal gases for warfare, and also of devising methods of protection against them. A forthcoming volume of the Medical History of the War will show that they had no chance with us when we really put our backs and brains into it. And that is what is meant by the need of earnestness.

We jog along comfortably so long as we are not troubled. Taken as a whole we are not very imaginative, and, unless we have been up against it cannot picture what sleeping sickness or any other important tropical malady really means—not only to humanity but to the welfare of our Commonwealth. If sleeping sickness could establish itself here and begin to worry us and frighten us we would soon be up in arms against it. Our mental lethargy would vanish and we would quickly find methods of defeating it, for the latent talent of this country is wonderful, as the German found to his cost in the late War. As, however, there is no way of bringing home the importance of tropical diseases to the masses by violent measures, and as education regarding them operates slowly, the necessary effort must be made by the comparatively few who do understand. They must make the Government appreciate the situation and carry conviction also to our masters of commerce, for it is on trade that our whole fabric depends. The British Empire Exhibition of 1924 is to make a great effort in this direction, but it is no use waiting till 1924.

As Sir William Pope says, it seems shameful that Great Britain should be content to play second fiddle to Germany in the matter of chemo-therapy. All honour to the Teuton for what he has accomplished in this field. He has reaped and is reaping his reward, but it is high time that the Briton should bestir himself, and, remembering his vast responsibilities, spare no effort to justify the position in which he stands, and in doing so benefit not only humanity but his own depleted coffers.

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